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MCGAW, MICHAEL M	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,006	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-97 and 110-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-97 and 110-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/15/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of Application Number 09/930,915. Claims 1-78 and 98-109 have been cancelled by preliminary amendment. Claims 79-97 and 110-115 are currently under examination.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 79-97 and 110-115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 79 contains many ambiguities making meaningful interpretation difficult at best. The wording of the claim, including the grammatical structure and most importantly the liberal usage of 'or' within the claims, renders them subject to numerous possibilities in their application. All claims directly or indirectly refer to claim 79.

Applicant uses the phrase "conservatively substituted" in claim 79. Applicant provides inconsistent definitions for this term in the specification. The definition on page 18 states "[t]he term 'conservative substitution' as used herein denotes that one amino acid residue has been replaced by another, biologically similar residue." It is not exactly clear what applicant means by biologically similar, though the subsequent examples do provide some guidance. Then on page 48 applicant tells us:

> Where a HBc sequence is truncated at the C-terminus beyond position 149 or at the N-terminus, or contains one or more deletions in the immunogenic loop, the number of substituted residues is proportionally different because the total length of the sequence is less that 149 residues. ***Deletions elsewhere in the molecule are considered conservative substitutions for purposes of calculation.*** (emphasis added)

To say that a deletion is a conservative substitution is not consistent with the prior definition requiring that one amino acid is replaced by another, biologically similar residue.

It is also not clear as to which sequence one compares to determine a conservative substitution. A generic HBc sequence is about 185 residues in length. On page 47 of the specification applicant discusses numerous sequences. It appears that the preferred sequence is that of subtype *ayw* from positions 1 to 149, but the applicant in no way limits himself to that sequence. Furthermore, applicant makes even this more vague when he indicates that this will be less any truncations due to terminal deletions. To then provide that portions of different sequences from different mammalian HBc proteins may be used really makes the issue hopelessly muddied.

In claim 79, part (c) it says that the chimer "contains a sequence of at least 6 amino acid residues from HBc position 135 to the HBc C-terminus..." It is not at all clear what is meant by this limitation. Furthermore, the HBc C-terminus is at approximately residue 185. Thus, it could be read as merely dictating a contiguous sequence of 5

residues from somewhere in the HBc sequence from position 135 to 185. In part 1(a) of the claim it states that we have "an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues..." So one could envision having the HBc sequence from residues 1-130 and then residues 174-178. It is known that residues ~130-150 are critical to form dimers. Pumpens et al (1995), as included by applicant as A16 on the information disclosure statement (IDS), says on page 66 that "[t]he C-terminal border for HBc sequences required for self-assembly [is] located between amino acids residues 139 and 144." Furthermore, if we include 174-178 we will have an Arginine-rich region which would potentially create nucleic acid binding. Is this merely meant to include a vast number of inoperable molecules within the scope of the claim or is the examiner misreading the limitation?

Likewise, it is not clear what applicant is claiming in claims 80 and 82. For example, in claim 80 applicant states that "Domain IV comprises zero through fourteen residues of a HBc amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III..." If the molecule contains zero residues from this region then they are missing the region mentioned above that is so critical for dimerization. Claim 80 depends on claim 79. Part (c) of claim 79 states that there are at least 6 amino acids residues from position 135 to the end. How can there now be zero residues? Likewise, part (d) of 82 says there are 5 to 14 from position 136 through 149. Five residues in claim 82 is inconsistent with at least 6 residues in claim 79. Thus, the particular limitation found in claim 79 is broadened rather than limited by the limitations in claims 80 and 82.

Applicant uses the word "contain" in phrases such as "contain a sequence..." in claim 79. The transitional term is being interpreted as open-language, synonymous with the term "comprising" or "containing".

In claims 79 applicant states that there is a "heterologous linker residue ... in the HBc immunodominant loop..." or simply a "heterologous linker residue". In the context of a single residue, how does one determine that this is 'heterologous', especially when one allows for conservative substitutions within the HBc sequence? Also, as is pointed out more fully below, the immunodominant loop already contains numerous residues that could be used as linker residues. Why then would one want to add additional linker residues?

The terms "of at least about" and/or "up to about" in claim 79 are relative terms which render the claim indefinite. These terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Appropriate correction is required.

Part (c) of claim 80 states "Domain III an HBC sequence from position 86 through position 135 peptide-bonded to residue 85..." Thus, residue 85 must be present. In part (b) it is stated "Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) at least 4 residues in a sequence of HBc positions 76 through 85 are present..." (emphasis added). Part (c) would indicate that residue 85 must be present while part (b) would indicate that 4 residues in a

sequence must be present. Therefore, residues 82-85 must be present. The claim is being interpreted accordingly.

Claim Rejections - 35 USC § 112, ¶1

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 79-97 and 110-115 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "Domain IV comprises (i) fourteen residues of a HBc amino acid residue sequence...", does not reasonably provide enablement for "Domain IV comprises (i) ***zero to*** fourteen residues of a HBc amino acid residue sequence..." as found in claim 80. Similarly, claim 79 part (c) provides that the HBc chimer contain[s] a sequence of at least 6 amino acids residues from HBc position 135 to the HBc C-terminus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention the invention commensurate in scope with these claims.

On page 126 of the specification it is indicated that particles were created in which a cys residue was added to position 149 of the HBc chimer. Applicant then goes on to explain, as previously shown by Zlotnick, et al. in 1997 (on applicants form 1449 as reference A29), that such particles are more stable than one in which there is no cys residue at position 149. This would be fourteen residues of a HBc amino acid residue sequence. It does not appear that applicant teaches that anything shorter will work.

Zero residues of an HBc sequence would result in a termination at position 135, which would then have a cys residue added at position 136. Metzger et al. (1998) (cited by applicant as A17) is cited as evidence that it is well-known that "HBc variants containing the first 139 or less residues are not able to assemble into particles, while variants containing 144 residues or more are still capable of assembling." (see pg. 587, col. 2, 1st full paragraph). Therefore, it is not expected that an HBc chimer containing zero residues from position 136 to 149 would even form capsids. It appears that truncations beyond 144 start to cause problems. Such problems could further be exacerbated by steric interference created by sequences attached to the C-termini. Also, as mentioned above, it is not just any amino acids from this region that are required, but the residues as found in positions immediately adjacent to residues 135 of the HBc molecule.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 79-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshikawa, A. et al. (1993) or Zlotnick et al. (1997).

Applicant claims a vaccine or inoculum where the particles are comprised of recombinant chimeric HBc protein molecules in various forms, such as containing a sequence of at least 135 of the N-terminal 150 amino acids, containing a heterologous

linker residue, or containing a peptide-bonded heterologous epitope. The HBc fusions contain one to ten cysteine (cys) residues ***within about*** 30 residues from the c-termini. The molecules should be substantially free of binding to nucleic acids, should self-assemble, should be more stable than similar molecules without the C-terminal cys residue.

Yoshikawa, A. et al. (1993) Journal of Virology, 67(10) p. 6064-6070 teach chimeric Hepatitis B core particles carrying antigenic epitopes of hepatitis C virus core protein. Figure 1 on page 6065 shows some of the chimeric proteins created.

pHBCx0, the first of the constructs from the top of Fig. 1, contained the n-terminal 149 amino acids of HBc fused to the residues found as coded in the multiple cloning site of the vector. That chimera had a cys residue within 4 residues of the N-terminal end. That sequence was expressed and used as a control to test the efficacy of the HBc-HCV fusions. (See for instance fig. 2) That HBc chimera was recognized by anti-HBc antibody but not by anti-HCV antibody.

Also created was the construct pHBCx1. This construct had the HCV core polypeptide (amino acid residues 1-180) fused to residue 149 of the HBc core molecule. Bukh, J. et al. (1994) Proc Natl Acad Sci U S A. 91(17):8239-43 is cited as evidence that the HCV core protein contains a conserved cys residue at position 172. (See pg. 8242, fig. 2) Thus, pHBCx1 had a cys residue within 8 amino acids of the C-terminus of the HBc-HCV chimer. Additionally, pHBC1-91 included residues 1-91 of HCV core peptide. It appears that residue 91 is generally a cys residue, though this residue is not

conserved across all genotypes. PHBC1-91 and pHBCx1 may bind nucleic acids by virtue of residues in the HCV core protein.

Yoshikawa, A. et al. teach two or more HBc core particle chimeras with cys residues at or near the C-terminal and definitely within about 30 residues of the C-terminal. One of the these displayed HCV core protein epitopes at the C-terminal end.

Specifically, Yoshikawa, A. et al. teach a recombinant hepatitis B core (HBc) protein molecule, pHBCx0, which is up to about 515 amino acid residues in length (actually for pHBCx0 ~173 aa's) that contains an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that includes either a peptide-bonded heterologous epitope and/or contains a sequence of 135 residues of the N-terminal 150 HBc amino acid residues, contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], contains a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus.

The chimeric polypeptides self-assembled into particles (see fig 4, g 6068) and meet the limitation as to the conserved amino acids. The pHBCx0 particles produced by Yoshikawa, A. et al. would be substantially free of binding to nucleic acids on expression in a host cell since the region from 150-183 (the protamine domain known to bind nucleic acid) was deleted. Applicant indicates in Example 6 on page 125 that HBc core molecules of 149 residues in length have added stability when a –terminal cysteine is added. That added stability can also come as a result of the cys residue in a

sequence added to the C-terminal end. Therefore, particles produced from pHBCx0 would be more stable than particles formed from an otherwise identical HBc chimer that lacks the C-terminal cys or in which the C-terminal cys residue present in the chimer is replaced by another residue.

Zlotnick et al. (1997) (Cited on applicant's IDS as A29) teach a recombinant hepatitis B core (HBc) protein molecule of less than 515 amino acid residues in length that contains an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule **and** that includes residues that can be used as linkers for a conjugated epitopes present in the HBC immunodominant loop. As to the three alternative limitations found in part (a) of claim 79, it contains a sequence of 135 residues of the N-terminal 150 HBc amino acid residues. Zlotnick's hepatitis B core (HBc) protein molecule contained one cysteine residue at the C-terminus of the molecule. Zlotnick's recombinant hepatitis B core (HBc) protein molecule contained a sequence of about 15 amino acid residues from HBC position 135 to the HBC C-terminus. Zlotnick's recombinant hepatitis B core (HBc) protein molecule self-assembled into particles (pg. 9558; 1st full paragraph) that are substantially free of binding to nucleic acids on expression in a host cell (pg. 9560; last full paragraph), and said particles being more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue (pg. 9558; 1st and 2nd full paragraphs).

Zlotnick's linker residues were not heterologous. It is not apparent why it should be of significance that the residues found in the immunodominant loop should, in fact, be heterologous when the immunodominant loop already contains many of the linker residues as recited in claim 17. Applicant, on page three of the specification, describes the immunodominant loop region as being at about residues 70-90. While it was not disclosed which subtype Zlotnick was working with, if one assumes for the purposes of example that Zlotick utilized subtype *ayw*, then there would be linker residues at positions 70 (Tyr), 77 (Glu), 78 (Asp) and 83 (Asp). Additional linkers might also be available at 60 (Cys), 91 (Tyr), and 96 (Lys).

Claims 79-80, 87, 110-111, 113-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Stahl et al. (1989).

Stahl et al. (1993) Proc. Natl. Acad. Sci., 86 p. 6283-6287 teach chimeric Hepatitis B core particles carrying antigenic epitopes of heterologous hepatitis B virus peptides. Figure 1 on page 6284 shows some of the chimeric proteins created. Many of the chimeras had both C-terminal and N-terminal fusions. Constructs such as HBcS111-156 had a C-terminal cys residue within one residue of the termini. The lengths of the constructs with the C-terminal cys residues varied from roughly 191 residues to 218 residues. Antigenicity of the constructs was shown on pages 6284-6285. Thus, Stahl also teaches methods of inducing an immune response with these particles. Stahl administered the particles with an adjuvant (pg. 6284, col. 1).

The particles produced by Stahl et al. would be substantially free of binding to

nucleic acids on expression in a host cell since the region from 145-183 (the protamine domain known to bind nucleic acid) was deleted. Applicant indicates in Example 6 on page 125 that HBc core molecules of 149 residues in length have added stability when a C-terminal cysteine is added. That added stability can also come as a result of the cys residue in a sequence added to the C-terminal end as indicated on page 128 of the specification. Therefore, particles produced from the constructs such as HBcS111-156 would be more stable than particles formed from an otherwise identical HBc chimer that lacks the C-terminal cys or in which the C-terminal cys residue present in the chimer is replaced by another residue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 79-80, 82-97, 110-111 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,990,085 in view of Zlotnick et al (1997).

Applicant claims a recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that (a) contains an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule. The sequence can include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBC immunodominant loop. The

sequence contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]. It contains a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus. The resulting chimer molecules contain no more than 20 percent conservatively substituted amino acid residues in the HBC sequence, self-assemble into particles that are substantially free of binding to nucleic acids on expression in a host cell, and are more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue.

One of the '085 patent's HBc chimeras utilized an internal insertion site at amino acid position 78 (see col.7, line 41). This chimera had a C-terminal truncation, ending at position 144 relative to the HBc sequence.

U.S. Patent No. 5,990,085 ('085 patent) to Ireland et al. (cited as A5 by applicant) teaches an inhibin-HBc fusion protein molecule of less than 515 amino acid residues in length that contains an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule. This protein molecule included a peptide-bonded heterologous epitope (ie. the inhibin insertion), contained one cysteine residue at position 107 of the HBc molecule [C-terminal cysteine residue(s)]. It contained a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus. One of Ireland's HBc chimeras utilized an internal insertion site at amino acid

position 78 (see col.7, line 41). This chimera had a C-terminal truncation, ending at position 144 relative to the HBc sequence.

Zhou et al. (1992) *Journal of Virology,* 66(9):5393-98 is cited as evidence that HBC has four Cys residues, one of which is located at position 107. Consequently, where a chimer, such as the '085 patent's inhibin-HBc fusion chimer, has a c-terminal truncation without the addition of exogenous amino acids, a Cys reside would be present 37 amino acids from the C-terminal end. Therefore, the '085 patent arguably satisfies the limitation that there be a Cys residue "about 30 residues from the C-terminus of the chimer molecule" and therefore would constitute anticipatory art under 102(b). In the alternative, these claims are presently rejected over U.S. Patent No. 5,990,085 in view of Zlotnick et al (1997).

The '085 patent indicates on line 65 of column 7 that the inhibin-HBc fusion protein self-assembled. As to claim 82, the limitation as to the ratio of absorbance would be met since the deletion from the region from 145-183 would ablate nucleic acid binding. As for limitations found in dependent claims, one of ordinary skill would be aware of the use of adjuvants and diluents (claims 87-97) various techniques of preparing the chimeras (claims 85-86) and routes of administration (claims 83-84). As for claims 110-111 and 113-115, the '085 patent teaches a method of inducing an immune response via subcutaneous and intraperitoneal immunization of mice and Latvian White gilts. (See cols. 9-10).

As mentioned above, one of the chimers had a cys residue within 37 amino acids from the C-terminal. It is not clear whether or not this meets the limitation of being

"about 30 residues from the C-terminus of the chimer molecule." If this phrase is strictly construed, then the '085 patent does not teach a C-terminal cysteine residue "about 30 residues from the C-terminus of the chimer molecule."

Zlotnick et al. (1997) teach adding a c-terminal cysteine residue to achieve a stabilizing effect.(See pgs. 9556 and 9558) Zlotnick's HBc chimera contained the HBc sequence from position 135-149 with a terminal cysteine at position 150, thus meeting the dual limitations of a chimer that contains (1) a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus and one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]. Zlotnick clearly demonstrates that the c-terminal particles are more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) (see page 9558, col. 1, first and second full paragraphs).

One of ordinary skill in the art would have been motivated to combine the teachings of the '085 patent teaching HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability.

One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 79-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995) in view of Zlotnick et al (1997).

Applicant's claims are as outlined above.

Pumpens (cited by applicant as A16) teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules of a variety of lengths up to about 515 amino acid residues in length. These chimers contain an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule (See for instance Fig. 1, pg. 64) that include a peptide-bonded heterologous epitope (Table 1, page 66) or a heterologous linker residue for a conjugated epitope present in the HBC immunodominant loop (see page 69, col. 1, last paragraph). Pumpens discloses that HBc chimeras with c-terminal truncations are capable of self-assembly and do not bind or 'pack' nucleic acid. (page 67, col. 1).

Pumpens makes two critical points on page 67. First, Pumpens reports that "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." Second, that "foreign insertions [at this site]

are not only possible but also exert a stabilizing effect on chimeric HBCΔ derivatives..." Pumpens does not teach adding a c-terminal cysteine residue to achieve the stabilizing effect.

Zlotnick et al. (1997) teach adding a c-terminal cysteine residue to achieve a stabilizing effect.(See pgs. 9556 and 9558) Zlotnick's HBc chimera contained the HBc sequence from position 135-149 with a terminal cysteine at position 150, thus meeting the dual limitations of a chimer that contains (1) a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus and one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]. Zlotnick clearly demonstrates that the c-terminal particles are more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) (see page 9558, col. 1, first and second full paragraphs).

One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining this various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability.

One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 79-82 and 110-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thornton et al. (U.S. Patent No. 5,143,726) in view of Zlotnick et al (1997).

Applicant claims an immunogenic particle wherein the linker residue is conjugated to a hapten.

U.S. Patent No. 5,143,726 to Thornton et al. (cited by applicant) teaches the use of HBc as an immunogenic carrier molecule where a polypeptide is linked to the carrier/core molecule through an amino acid side chain on the core molecule (see abstract). Zlotnick teaches methods of use of HBc core molecules.The '726 patent used the full-length HBc molecule. Thus it would bind endogenous nucleic acids. Thornton does not teach HBc as a carrier epitope where the resulting molecule is substantially free of binding to nucleic acid.

Zlotnick teaches a recombinant HBc molecules that do not bind nucleic acid and with enhanced stability. Zlotnick et al. teach a recombinant hepatitis B core (HBc) protein molecule (immunogenic particle) with a C-terminal cysteine as variously

described above (see particularly the section relating to 102(b)). Zlotnick teaches that these molecules are capable of assembling into capsids and that they are more stable than molecules without the C-terminal cysteine residue (pg. 9558). Zotnick also indicates that these C-terminal truncations with the cysteine residue do not package RNA within their capsids.

One of ordinary skill in the art would have been motivated to combine the teachings of Thornton with that of Zlotnick because Zlotnick teaches that a truncated molecule loses the ability to pack endogenous nucleic acid while the addition of the C-terminal cysteine greatly enhances the stability of the resulting truncated particles. One of ordinary skill in the art would have expected achieve a more stable HBc molecule that could present an epitope via a side-chain with a greatly diminished risk of carrying nucleic acids from the cell in which the particles were produced. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

Claims 79-97 and 110-115 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of copending Application No. 10/732,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-69 are drawn to the same subject matter, e.g., recombinant chimer HBC protein molecules

that have C-terminal cysteines, self-assemble into particles, and have improved particle stability, as are claims 1-46 of 10/732,862, differing only in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Neirynck, et al. (1999) (cited by applicant as A30) teach HBc core protein as an epitope carrier for influenza M2 protein. Neirynck indicates that it may be administered intraperitonealy or intranasally. (page 1160) Adjuvants including muramyl dipeptide and monophosphoryl lipid A were used (See page 1162, col. 2)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. McKelvey

Saturday, September 18, 2004

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1800